REMARKS

Claims 1-16 are pending in this application. Claims 1-16 are canceled herein without prejudice to pursuit of their prosecution in a continuation application. New claims 17-26 are added herein. Support for these new claims is found in the language of the original claims and throughout the specification, as set forth below. Applicants assert that no new matter is added by these new claims and their entry and consideration are respectfully requested. In light of these new claims and the following remarks, applicants respectfully request consideration of this application and allowance of the pending claims to issue.

I. Priority

The Office Action states that the pending claims have not been awarded the filing date of U.S. provisional application no. 60/162, 390 (the '390 application), filed October 29, 1999, from which the present application claims priority. Specifically, the Office Action states that the claimed subject matter is not present in the '390 application, which the Examiner states is directed to an association between diseases, such as cardiovascular diseases, and the presence of a short allele of the serotonin transporter gene promoter. It is further the Examiner's position that the '390 application does not demonstrate an association between cardiovascular diseases, or any diseases, in response to stress and the long allele of the serotonin transporter gene promoter.

Applicants respectfully point out that the pending claims are indeed entitled to the filing date of October 29, 1999 of the '390 application because the '390 application does indeed disclose the claimed subject matter and also demonstrates an association between cardiovascular diseases and other diseases in response to stress and the long allele of the serotonin transporter gene promoter.

Applicants direct the Examiner's attention to the Summary of the Invention of the '390 application, which states as follows.

> The present invention is based on the recognition that by assessing genotypes (long vs. short alleles) of a polymorphism of the promoter region of the gene that encodes the serotonin transporter (5HTTLPR), one can identify persons who are more sensitive to stress and, therefore, at higher risk of developing a broad range of diseases. Thus, the present invention provides a method of screening subjects for disease risk. The method comprises determining the serotonin transporter gene promoter genotype (with respect to long and short alleles thereof) of a subject. The serotonin transporter gene promoter genotype is used to indicate whether or not the subject is at increased risk of disease. The method is particularly adapted to screening for risk of disease in response to stress, and accordingly can be used to indicate interventions that manage stress, and hence reduce disease risk, in susceptible or higher-risk individuals.
>
> In one particular embodiment, the method comprises determining the presence of at least one (and preferably two) serotonin transporter gene promoter short allele in a subject. The presence of at least one serotonin transporter gene promoter short allele (and particularly two short alleles) indicates the said subject is at increased risk of disease, as compared to a subject with no short alleles, or a subject with only one short allele.

As would be reasonably apparent to one of skill in the art, the summary of the invention set forth in the '390 application states that the invention is directed to identifying genotypes (either long or short alleles) of a polymorphism of the serotonin transporter gene promoter and thus identifying subjects with greater sensitivity to stress and therefore greater susceptibility to developing a variety of diseases associated with stress. It is further stated in the '390 application that the method comprises determining the serotonin transporter gene promoter genotype of a subject (either long or short allele) and using that genotype to indicate whether or not a subject is at increased risk of disease. The '390 application then provides an example, which is clearly identified as only one embodiment of the invention, wherein the presence of a serotonin transporter gene promoter short allele is indicative of an increased risk of disease. Thus, applicants submit that one of skill in the art would reasonably conclude from this disclosure that the

invention is directed to identifying either a short or long allele genotype in the serotonin transporter gene promoter of a subject and identifying an association with either genotype and increased sensitivity of the subject to stress and thus increased susceptibility to disease associated with stress.

Furthermore, applicants direct the Examiner's attention to claim 1 of the '390 application, which sets forth a method of screening human subjects for disease risk by determining the serotonin transporter gene promoter genotype in a subject that is indicative of whether the subject is at increased risk of disease. This claim is broader than dependent claim 2 of the '390 application, which sets forth the embodiment where the determining step comprises determining the presence of at least one short allele. Thus, it is apparent that the invention set forth in the '390 application covers detection of both long and short alleles and is more inclusive than the Examiner describes.

The '390 application also provides data to demonstrate an association between the long allele genotype and increased sensitivity to stress, as presented in Example 1 on pages 4 and 5 of the '390 specification. In particular, studies are described in this example wherein test subjects were assessed for various physiological responses upon exposure to different stressors (reading text out loud, anger and sadness recall). Data from these studies revealed that subjects with an l/l or l/s genotype had higher CSF 5HIAA levels than subjects with an s/s genotype and that subjects with higher 5HIAA levels also had higher basal plasma prolactin, decreasing plasma cortisol levels during the stress protocol following tryptophan infusion and larger heart rate and blood pressure reactivity to stress with sham tryptophan depletion that is attenuated by active depletion. Thus, these studies, as described in the '390 application, demonstrate an association between the long allele genotype and increased sensitivity to stress, as well as increased physiological response to stress, thereby demonstrating an associate between the long allele genotype and diseases associated with an increased physiological response to stress, such as cardiovascular diseases.

Thus, it is apparent that the subject matter of the claimed invention is supported in the disclosure of the '390 application and is thus entitled to the October 29, 1999 filing date and applicants respectfully request that the Examiner withdraw previous comments

regarding a lack of priority and acknowledge on the record the priority status demonstrated by applicants.

II. Rejection under 35. U.S.C. § 112, first paragraph

The Office Action states that claims 1-16 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Specifically, the Office Action states that the specification is enabling for a method of screening human subjects for increased risk of coronary heart disease in response to smoking by detecting the presence of at least one serotonin transporter gene promoter long allele, but that it is allegedly not enabling for a method of screening human subjects for increased risk of disease in general in response to any stress, or broadly any cardiovascular disease, infectious disease, cancer, autoimmune disease, delayed wound healing or gastrointestinal disease, or for increased risk of infectious disease in general or any specific infectious disease, by detecting the presence of at least one serotonin transporter gene promoter long allele. The Examiner then presents an analysis of the claimed invention according to the factors set forth in *In re Wands*.

The claims as presented herein recite a method of identifying a subject having an increased likelihood of having an increased sensitivity to stress, having an increased likelihood of having an increased physiological response to stress, and having an increased likelihood of developing a cardiovascular disease associated with an increased physiological response to stress, comprising detecting the presence of at least one serotonin transporter gene promoter long allele in the subject. Dependent claims further recite that the cardiovascular disease can be hypertension, coronary heart disease, stroke or an atrial or ventricular arrhythmia. Support for these claims is found throughout the specification, at least, for example, on page 5, lines 27-29.

The claimed invention is clearly enabled in the specification as filed, on the basis that the Examples section provides the results of several studies that were carried out to demonstrate that the presence of at least one serotonin transporter gene promoter long

allele is associated with an increased sensitivity to stress, as well as an increased physiological response to stress. Thus, applicants provide numerous working examples whereby several different physiological parameters were measured in individuals who were subjected to specific stressors and the serotonin transporter gene promoter genotype was also determined in these individuals. As described in Examples 2-6 of the specification, the applicants identified an association between increased sensitivity to stress and increased physiological response to stress of a subject and the presence of at least one long allele of the serotonin transporter gene promoter in that subject.

Furthermore, the present invention is enabled for the identification of a subject having an increased likelihood of developing a cardiovascular disease associated with an increased physiological response to stress, on the basis that it was well known to one of ordinary skill in the art at the time this invention was made that cardiovascular disease and risk factors associated with cardiovascular disease are associated with an increased physiological response to stress [see, e.g., studies describing the association of stress and coronary artery disease in Rozanski et al. ("Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy" *Circulation* 99:2192-2217 (1999)); studies describing the association of stress and atherosclerosis in Kamarck et al. ("Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men" *Circulation* 96:3842-3848 (1997)) and Matthews et al. ("Stress-induced pulse pressure change predicts women's carotid atherosclerosis" *Stroke* 29:1525-1530 (1998)); and studies describing the association of stress and stroke in Everson et al. ("Anger expression and incident stroke: Prospective evidence from Kuopio Ischemic Heart Disease Study" *Stroke* 30:523-528 (1999)) and Everson et al. ("Stress-induced blood pressure reactivity and incident stroke in middle-aged men" *Stroke* 32:1263-1270 (2001)); a copy of each of which is included herewith].

Thus the present invention clearly links the two associations, that of 1) an increased sensitivity or an increased physiological response to stress and the presence of

at least one serotonin transporter gene promoter long allele, and 2) an increased sensitivity or an increased physiological response to stress and the incidence of cardiovascular disease. It would be readily apparent to one of ordinary skill in the art that the present invention thus establishes an association between the presence of at least one serotonin transporter gene promoter long allele and an increased likelihood of developing cardiovascular disease and that undue experimentation would not be required to identify this association and thus to carry out the methods of this invention. For these reasons, applicants assert that the present invention is adequately enabled and respectfully request the withdrawal of this rejection and the allowance of the pending claims to issue.

III. Rejection under 35 U.S.C. § 102(b)

The Office Action states that claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Arinami et al.

As set forth above, applicants submit that the claimed subject matter is entitled to the filing date of October 29, 1999 of the '390 application from which the present application claims priority. On that basis, the Arinami et al. publication, which is dated June, 1999, is therefore allegedly only a prior art reference, if at all, under 35 U.S.C. § 102(a).

Applicants assert that the Arinami et al. publication is not available as a prior art reference for rejecting claims of the present invention, on the basis that applicants conceived of and reduced to practice the claimed invention prior to the publication date of the Arinami et al. reference. Specifically, applicants provide herein a Declaration under 37 CFR § 1.131 whereby the inventor, Dr. Redford Williams, declares that the conception and reduction to practice of the claimed invention was prior to June, 1999, thereby rendering the Arinami et al. reference unavailable as prior art to the present invention. Thus, this rejection has been rendered moot and applicants respectfully request its withdrawal.

In view of the foregoing amendments and remarks, applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In the event that the Examiner fails to find allowable subject matter upon review of the claims as presented herein, applicants respectfully request a telephone interview to include the Examiner and the Examiner's supervisor, prior to the issuance of any further actions for this application.

A check in the amount of $405 ($225 fee for two month extension of time and $180 fee for supplemental Information Disclosure Statement) is enclosed. This amount is believed to be correct. However, the Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

Mary L. Miller
Registration No. 39,303

USPTO Customer No. 20792
Myers Bigel Sibley & Sajovec
Post Office Box 37428
Raleigh, North Carolina 27627
Telephone (919) 854-1400
Facsimile (919) 854-1401
Enclosure: F. Fumeron et al.

CERTIFICATE OF EXPRESS MAILING UNDER 37 CFR 1.10
"Express Mail" mailing label number: EV854928458US
Date of Deposit: March 31, 2006
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Tracy Wallace